105 and 107, respectively. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth above the amendment to the claims and specification in clean form in Appendix A, with marked up amendments indicated with brackets and underlining.

In addition to co-pending application serial Nos. 08/791,391 and 08/790,540, Applicants bring to the Examiner's attention co-pending application serial No. 09/016,061.

Objection to the Claims

The objection to claims 3, 6, 9 and 12 as being in improper dependent form is respectfully traversed. Claims 3, 6, 9 and 12 have been rewritten in independent form. Accordingly, Applicants submit that this objection has been rendered moot and respectfully request that this objection be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1-3, 13, 14, 25 and 26 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Office Action asserts that there is insufficient guidance as to the predictability of enabling LM609 antibodies that retain their binding activity to $\alpha_v\beta_3$.

Applicants submit that the specification provides sufficient description and guidance to enable the claimed antibodies and encoding nucleic acids. Claims 1 and 25, as amended, recite functional characteristics of the claimed antibodies, in particular, that the grafted antibody or functional fragment thereof has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Furthermore, the specification teaches exemplary antibodies comprising the specifically recited CDRs and having the recited functional activity (see Example VIII, pages 102-108 and Tables 11, 13 and 15). Accordingly, Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed antibodies and encoding nucleic acids and respectfully request that this rejection be withdrawn.

The rejection of claims 1, 3, 4, 6, 7, 9, 10, 12-20, and 25-33 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for "functional fragment" is respectfully traversed. Applicants submit that the specification provides sufficient description and guidance to enable claims reciting "functional fragment." The specification teaches that a functional fragment refers to a portion of a grafted antibody that retains some or all of the $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity and/or integrin $\alpha_v\beta_3$-inhibitory activity (page 15, line 21, to page 16, line 7). Furthermore, claims 1, 3, 4, 6, 7, 9, 10, 12 and 25 have been amended to recite that the functional fragment has the functional activity of having integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Accordingly, Applicants

respectfully submit that the specification provides sufficient description and guidance to enable the claims reciting functional fragment and respectfully request that this rejection be withdrawn.

The rejection of claims 1-3, 6, 9, 12-14, 25, 26 and 33 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description is respectfully traversed. The Office Action alleges that claims reciting "substantially the same," directed to grafted antibodies comprising one particular CDR, and reciting the phrase "having the sequence" as allegedly lacking sufficient written description.

Applicants submit that the specification provides sufficient description and guidance to convey to one skilled in the art that the inventors were in possession of the claimed invention at the time the application was filed. Regarding the phrase "substantially the same," as recited in claims 3, 6, 9 and 12, these claims are directed to enhanced LM609 grafted antibodies having substantially the same sequence as a grafted antibody comprising a specifically recited CDR referenced as a SEQ ID NO. Thus, the claims recite specific structural characteristics of the claims. These claims, as amended, specifically recite functional characteristics of the claimed antibodies, that is, having integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Furthermore, the specification teaches that "substantially the same," when used in reference to a nucleotide or amino acid sequence, refers to a sequence that shows a

considerable degree, amount or extent of sequence identity when compared to a reference sequence (see page 13, line 25, to page 15, line 2). Accordingly, Applicants respectfully submit that the specification provides sufficient description and guidance for the claimed grafted antibodies having substantially the same sequence.

Regarding the alleged lack of written description for antibodies comprising one particular CDR selected from a Markush group, claims 1 and 25, as amended, are directed to an antibody having a CDR selected from a group of CDRs having specifically recited SEQ ID NOS, where the antibody has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. The claimed antibody does not rely on a single CDR but, rather, comprises a particular CDR, and the antibody has functional binding or inhibitory activity for $\alpha_v\beta_3$.

Regarding claim 33, which recites the phrase "having a nucleotide sequence," the claim recites specific SEQ ID NOS, and each of these SEQ ID NOS is taught in the specification (see Tables 12 and 14 on pages 105 and 107, respectively). Therefore, Applicants respectfully submit that the specification provides sufficient written description for this claim.

Applicants submit that the specification provides sufficient written description for the claimed antibodies and encoding nucleic acids. Therefore, Applicants respectfully request that this rejection be withdrawn.

Regarding the assertion in the Office Action that the LM609 antibody is required to practice the invention, Applicants submit that the nucleotide sequence and deduced amino acid sequence of LM609 heavy chain variable region (SEQ ID NOS: 5 and 6, respectively) and LM609 light chain variable region (SEQ ID NOS:7 and 8, respectively) are disclosed in the specification (see Figure 2 and page 5, lines 14-23). Furthermore, the specification teaches methods of grafting LM609 CDRs (page 17, line 15, to page 18, line 12; page 18, line 24, to page 19, line 7; page 22, line 20, to page 23, line 9; page 34, line 30, to page 35, line 24; and Example V, pages 79-83) as well as methods for making and identifying antibodies having enhanced activity (see page 40, line 9, to page 46, line 26, and Examples VI-VIII, pages 83-108). It is the sequence of LM609 CDRs and substituted LM609 CDRs, including the substituted LM609 CDRs specifically recited in the claims, that are required to practice the claimed invention and are disclosed in the specification. Using the disclosed nucleotide sequences of the LM609 heavy and light chain variable regions, which provide antibody specificity, one skilled in the art can readily obtain an LM609 grafted antibody or functional fragment thereof using methods well known in the art. Thus, the disclosure of the nucleotide sequence of the LM609 heavy and light chain variable regions is all that is necessary to practice the invention as claimed.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-20 and 25-33 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully

traversed. Applicants respectfully submit that the claims reciting "LM609" are clear and definite. Although Applicants believe that the meaning of "LM609" is clear in view of the teachings in the specification, the claims reciting LM609 have been amended to recite structural characteristics of LM609. In particular, the claims recite that LM609 refers to the murine antibody having the heavy chain variable region amino acid sequence referenced as SEQ ID NO:6 and the light chain variable region amino acid sequence referenced as SEQ ID NO:8. Therefore, Applicants respectfully submit that the meaning of LM609 is clear and definite and request that this rejection be withdrawn.

Regarding claims reciting the term "enhanced," Applicants submit that the meaning of this term is clear and definite. The specification teaches that "enhanced" means that a functional characteristic of the antibody has been altered or augmented compared to a reference antibody so that the antibody exhibits a desirable property or activity (page 16, line 8, to page 17, line 5). Accordingly, in view of the teachings in the specification, Applicants maintain that the term "enhanced" is clear and definite. Therefore, Applicants respectfully request that this rejection be withdrawn.

Regarding the phrase "substantially the same," Applicants submit that the meaning of this phrase is clear and definite. In particular, the specification teaches that "substantially the same," when used in reference to a nucleotide or amino acid sequence, refers to a sequence that shows a considerable degree, amount or extent of sequence identity when

compared to a reference sequence (see page 13, line 25, to page 15, line 2). Therefore, Applicants respectfully submit that the meaning of this phrase is clear in view of the teachings in the specification and request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102

The rejection of claims 1-20 and 25-33 under 35 U.S.C. § 102(a) as allegedly anticipated by Huse et al., WO 98/33919, is respectfully traversed. The Office Action asserts that SEQ ID NOS:33, 34, 89, 90, 101, 102, 107, 108, 109, 110, 111 and 112 are disclosed in WO 98/33919. The Office Action further asserts that the claimed functional limitations would be inherent properties of the referenced humanized LM609 antibodies.

Applicants submit that Huse et al. does not teach the claimed antibodies and encoding nucleic acids. Regarding the assertion of particular SEQ ID NOS disclosed in Huse et al., Applicants respectfully point out that none of the specific SEQ ID NOS:101-112 were disclosed in Huse et al. With respect to claims 1, 3 and 25, Applicants point out that each of these claims requires that the antibody have a CDR selected from SEQ ID NOS:104, 106 or 110. Since none of these specific SEQ ID NOS were disclosed in Huse et al., Huse et al. cannot anticipate these claims.

With respect to claims 4, 6, 7, 9, 10, 12, 27, 29 and 31, each of these claims requires either SEQ ID NO:104 or 106, or both. Similarly, each of new independent claims 34, 38 and 42

requires either SEQ ID NO:104 or 106. Since Huse et al. does not teach either of SEQ ID NOS:104 or 106, which is acknowledged in the Office Action, Huse et al. cannot anticipate these claims.

Applicants respectfully submit that Huse et al. does not teach the claimed antibodies having the specifically recited SEQ ID NOS:104, 106 and 110. Absent such a teaching, Huse et al. cannot anticipate the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 1-20 and 25-33 under 35 U.S.C. § 102(b) as allegedly anticipated by Wu et al., Proc. Natl. Acad. Sci. USA 95:6037-6042 (1998), is respectfully traversed. Applicants respectfully submit that Wu et al. does not teach the claimed antibodies and encoding nucleic acids.

With respect to claims 1, 3 and 25, Applicants point out that each of these claims requires that the antibody have a CDR selected from SEQ ID NOS:104, 106 or 110. Since none of these specific SEQ ID NOS were disclosed in Wu et al., Wu et al. cannot anticipate these claims.

With respect to claims 4, 6, 7, 9, 10, 12, 27, 29 and 31, each of these claims requires either SEQ ID NO:104 or 106, or both. Similarly, each of new independent claims 34, 38 and 42 requires either SEQ ID NO:104 or 106. Since Wu et al. does not teach either of SEQ ID NOS:104 or 106, Wu et al. cannot anticipate these claims.

Applicants respectfully submit that Wu et al. does not teach the claimed antibodies having the specifically recited SEQ ID NOS:104, 106 and 110. Absent such a teaching, Wu et al. cannot anticipate the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 3, 6, 9 and 12 under 35 U.S.C. § 102(e) as allegedly anticipated by Brooks et al, U.S. Patent No. 5,75,230, is respectfully traversed. Applicants respectfully submit that Brooks et al. does not teach the claimed antibodies. Claims 3, 6, 9 and 12 are directed to enhanced LM609 grafted antibodies having substantially the same sequence as an enhanced LM609 grafted antibody comprising at least one CDR having SEQ ID NOS:104, 106 or 110. In contrast, Brooks et al. does not teach any of the specifically recited SEQ ID NOS:104, 106 or 110, nor any other LM609 sequence.

Furthermore, Brooks et al. does not teach or suggest an enhanced LM609 grafted antibody. As taught in the specification, an enhanced LM609 grafted antibody means that a functional characteristic of the antibody has been altered or augmented compared to a reference antibody so that the antibody exhibits a desirable property or activity (page 16, line 8, to page 17, line 5). Exemplary enhanced activities include, for example, higher or lower affinity binding, increased or decreased association or dissociation rates, or increased stability relative to a reference antibody (page 16, lines 14-20). In contrast, Brooks et al. does not teach an enhanced LM609 grafted antibody. Applicants respectfully submit that Brooks et al., at

most, indicates that humanized forms of LM609 may be made. Brooks et al. appears to describe the desirability of humanizing LM609 (column 17, line 62, to column 18, line 3), in contrast to Applicants' explicit teachings of methods for making humanized LM609 grafted antibodies that have enhanced activity.

Applicants submit that Brooks et al. does not teach the claimed enhanced antibodies having integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity and CDRs having specifically recited SEQ ID NOS. Therefore, Applicants respectfully submit that Brooks et al. cannot anticipate claims 3, 6, 9 or 12 and request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

The rejection of claims 1-20 and 25-33 under 35 U.S.C. § 103 as allegedly obvious over Brooks et al., *supra*, or Wu et al., *supra*, in view of known gene cloning and expression strategies for deriving recombinant antibodies is respectfully traversed. Applicants submit that the claimed antibodies and encoding nucleic acids are unobvious over Brooks et al. or Wu et al., alone or in combination with known methods of gene cloning.

Applicants' claims are directed to antibodies and encoding nucleic acids, and each of the claims recites at least one CDR having a specific SEQ ID NO. In contrast and as described above, Brooks et al., alone or in combination with known methods of gene cloning, does not teach or suggest the

claimed CDRs having SEQ ID NOS:104, 106 or 110. At best, Brooks et al. appears to describe the desirability of humanizing LM609 but provides no teaching or suggestion of the LM609 sequences disclosed in the above-identified application. Furthermore, Brooks et al. does not teach or suggest any of the specifically recited CDRs, which have at least one amino acid substitution compared to wild type LM609 (see Tables 11 and 14 on pages 104 and 106, respectfully). Moreover, Brooks et al. provides no teaching or suggestion of mutating CDRs and screening for integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity, as taught by Applicants. Furthermore, known methods of gene cloning cannot cure the deficiencies of Brooks et al.

Applicants submit that the claimed antibodies and encoding nucleic acids are unobvious over Brooks et al., alone or in combination with known methods of gene cloning. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Regarding Wu et al., Applicants respectfully submit that Wu et al., alone or in combination with known methods of gene cloning, cannot render the claimed antibodies and encoding nucleic acids obvious. In contrast and as described above, Wu et al. does not teach or suggest any of the specifically recited SEQ ID NOS:104, 106 or 110. Absent such a teaching or suggestion, Wu et al., alone or in combination with known methods of gene cloning, cannot render the claimed antibodies and encoding nucleic acids obvious.

Furthermore, Wu et al., alone or in combination with known methods of gene cloning, does not teach or suggest the unexpected properties of the claimed antibodies. In particular, the specification teaches that the grafted antibody variant 6H6LH, which comprises SEQ ID NOS:34, 102, 106, 108, 112 and 90 (Tables 11 and 13) and corresponds to claims 4 and 27 and new claim 34, had the unexpected property of reduced proteolysis (page 102, lines 20-25). Furthermore, the grafted variant 2236/6H6LH, which comprises SEQ ID NOS:34, 102, 106, 110, 112, and 90 and corresponds to claims 7 and 29 and new claim 38, and variant 2236-38/6H6LH, which comprises SEQ ID NOS:34, 104, 106, 110, 112, and 90 and corresponds to claims 10 and 31 and new claim 42, had the unexpected property of increased affinity (lower K_d) relative to the parental 6H6LH variant (see Table 15, page 108). Based on the description in Wu et al., alone or in combination with known methods of gene cloning, one skilled in the art would have had no reasonable expectation for successfully generating the claimed antibodies having the specifically recited SEQ ID NOS, reduced proteolysis and/or increased affinity absent the screening and testing taught in the specification.

Applicants respectfully submit that the claimed antibodies and encoding nucleic acids are unobvious over Wu et al., alone or in combination with known methods of gene cloning. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Double Patenting

Claims 1-20 and 25-31 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over the pending claims of copending U.S. application serial Nos. 08/791,391 and 08/790,540. The Office Action asserts that the claims are directed to the same or similar LM609 antibody and variants. Applicants respectfully traverse the double patenting rejection and submit that the claimed antibodies and encoding nucleic acids of the present invention are unobvious over the claims pending in U.S. application serial Nos. 08/791,391 and 08/790,540. In particular, neither of these applications teaches or suggests the claimed antibodies having CDRs with the specifically recited SEQ ID NOS:104, 106 or 110. Absent such a teaching or suggestion, Applicants respectfully submit that neither of application serial Nos. 08/791,391 or 08/790,540 can render obvious the claimed antibodies reciting SEQ ID NOS:104, 106 or 110. Accordingly, Applicants respectfully request that the provisional obviousness-type double patenting rejection be withdrawn.

Provisional Rejection Under 35 U.S.C. § 103

Claims 1-20 and 25-33 stand provisionally rejected under 35 U.S.C. § 103 as allegedly obvious over copending U.S. application serial Nos. 08/791,391 and 08/790,540. Applicants respectfully traverse the provisional obviousness rejection essentially for the reasons described above for double patenting. In particular, neither of these applications teaches or suggests

the claimed antibodies having CDRs with the specifically recited SEQ ID NOS:104, 106 or 110. Absent such a teaching or suggestion, Applicants respectfully submit that neither of application serial Nos. 08/791,391 or 08/790,540 can render obvious the claimed antibodies reciting SEQ ID NOS:104, 106 or 110. Accordingly, Applicants respectfully request that the provisional obviousness rejection be withdrawn.

Regarding Antibodies Considered Free of the Prior Art

The Office Action indicates that the antibodies comprising V_H CDR1 referenced as SEQ ID NO:34, V_H CDR2 referenced as SEQ ID NO:102/104, and V_H CDR3 referenced as SEQ ID NO:106 and nucleic acids comprising V_H CDR1 referenced as SEQ ID NO:33, V_H CDR2 referenced as SEQ ID NO:101/103, and V_H CDR3 referenced as SEQ ID NO:105 are free of the prior art. The Office Action invites Applicants to distinguish the teachings of Wu et al. from the instant claims.

For the reasons described above, Wu et al. does not teach or suggest any of the specifically recited SEQ ID NOS:104, 106 or 110 and, accordingly, cannot render the claimed antibodies and encoding nucleic acids obvious. In addition, Wu et al. does not teach or suggest the unexpected properties of the claimed antibodies. In particular, the specification teaches that the grafted antibody variant 6H6LH, which comprises SEQ ID NOS:34, 102, 106, 108, 112 and 90 (Tables 11 and 13) and corresponds to claims 4 and 27, had the unexpected property of reduced proteolysis (page 102, lines 20-25). Furthermore, the grafted

variant 2236/6H6LH, which comprises SEQ ID NOS:34, 102, 106, 110, 112, and 90 and corresponds to claims 7 and 29, and variant 2236-38/6H6LH, which comprises SEQ ID NOS:34, 104, 106, 110, 112, and 90 and corresponds to claims 10 and 31, had the unexpected property of increased affinity (lower K_d) than the parental 6H6LH variant (see Table 15, page 108). Moreover, Wu et al. does not teach or suggest the claimed antibodies with six specifically recited CDRs referenced as SEQ ID NOS. Based on the description in Wu et al., one skilled in the art would have had no reasonable expectation for successfully generating the claimed antibodies having the specifically recited SEQ ID NOS, reduced proteolysis and/or increased affinity absent the screening and testing taught in the specification. Accordingly, Wu et al. cannot render any of the claims obvious.

Applicants point out that claims 4, 7, 10, 27, 29 and 31 and new claims 34, 38 and 42 recite specific amino acid SEQ ID NOS for each of the six CDR positions of the claimed antibodies, and each recites at least one of the CDRs not taught or suggested by Wu et al., SEQ ID NOS:104, 106 and 110. Furthermore, new claims 37, 41 and 45 are directed to nucleic acids encoding antibodies, and the claims recite specific nucleic acid SEQ ID NOS for each of the six CDR positions. Wu et al. does not teach or suggest any of the specific combinations of CDR amino acid or nucleic acid sequences recited in the claims.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

December 21, 2001
Date

Deborah L. Cadena
Registration No. 44,048
Telephone No.: (858) 535-9001
Facsimile No.: (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122
USPTO CUSTOMER NO. 23601